REMARKS

I. Status Summary

Claims 5, 8-17, and 22-25 are pending in the instant application. Claims 9-17 are withdrawn from consideration as being drawn to a nonelected invention, and Claims 5, 8, and 22-25 have been examined.

Claims 5, 8, and 22-25 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gunzburg et al. (*Nature*, 364, 154-158, (1993); hereinafter "Gunzburg"), U.S. Patent No. 5,658,775 to Gilboa (hereinafter "the '775 Patent"), and Vile et al. (*Cancer Research*, 53, 962-967, (1993); hereinafter "Vile").

Claim 5 has been amended herein to add clarifying punctuation and to more clearly define the currently claimed subject matter by specifying that promoter conversion occurs upon infection of a target cell. Support for the amendment can be found in the specification as filed, particularly starting at page 6, line 1 to page 7, line 10, which describes that promoter conversion occurs when the vector enters the target cell. No new matter has been added.

Reconsideration of the application based on the amendments and remarks set forth herein below is respectfully requested.

II. Response to the Obviousness Rejection

Claims 5, 8, and 22-25 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gunzburg, the '775 Patent, and Vile. According to the Patent Office, the claims are drawn to a recombinant replication-defective retroviral vector capable of promoter conversion comprising a 5' LTR comprising the structure U3-R-U5, a first coding sequence encoding a therapeutic peptide, a second sequence encoding a peptide with Sag activity linked to a promoter active in B and/or T cells, and a 3' LTR comprising a completely or partially deleted U3 region that comprises a tissue-specific promoter that regulates the expression of the first coding sequence, followed by R-U5. *See* Official Action, bottom of page 2 to the top of page 3.

The Patent Office asserts that the difference between the presently claimed subject matter and the teachings of Gunzburg and the '775 Patent is "the tissue

specific promoter that replaces the 3' LTR and the B and/or T cell active promoter encoding Sag." *See* Official Action, page 3. The Patent Office further contends that this deficiency is remedied by Vile, which teaches retroviral vectors that express therapeutic genes with tissue specific promoters.

Thus, the Patent Office asserts that one of skill in the art would have been motivated to use a tissue specific promoter to express the therapeutic gene specifically in a tissue of interest, to express Sag specifically with a T and/or B cell specific promoter to optimize Sag in those cells for proliferation, and that one would have been motivated to regulate the expression of the therapeutic gene and Sag separately. The Patent Office further asserts that one of skill in the art would have had a reasonable expectation of success expressing a tissue specific promoter in the 3' LTR to regulate the expression of the first coding sequence because the '775 Patent teaches "replacing the 3' U3 region with any heterologous promoter and heterologous sequence". *See* Official Action, page 3.

After careful consideration of the rejection and the Patent Office's bases therefor, the applicants respectfully traverse the rejection and submit the following remarks.

II.A. The Combination of Gunzburg, the '775 Patent, and Vile Does Not Disclose or Suggest a Retroviral Vector as Claimed in the Instant Application

Initially, applicants respectfully traverse the Patent Office's assertion that the difference between the claimed vectors and the vectors of Gunzburg and the '775 Patent is the tissue specific promoter that replaces the 3' LTR and the B and/or T cell active promoter encoding Sag. Applicants respectfully submit that claim 5 recites *inter alia* a retroviral vector that is replication-defective and comprises the following elements in 5' to 3' order:

(a) a 5' LTR;

(b) a first coding sequence encoding a therapeutic polypeptide;

(c) a second coding sequence encoding a peptide with Sag activity operably linked to a B cell and/or T cell promoter; and

(d) a 3' LTR comprising a completely or partially deleted U3 region,

wherein said completely or partially deleted U3 region is replaced by a polylinker sequence comprising at least one unique restriction site into which is inserted one or more non-coding sequences selected from regulatory elements and promoters, which, upon infection of a target cell, regulate expression of the first coding sequence after promoter conversion.

Applicants respectfully submit that claim 5 recites a non-self-inactivating vector, the body of which contains two coding sequences. The first coding sequence encodes a therapeutic polypeptide and is promoterless in the vector, and the second encodes a peptide with Sag activity that is operatively linked to a B cell- and/or T cell-specific promoter. Thus, the instantly claimed vectors can provide both a peptide with Sag activity to facilitate B-cell and/or T-cell proliferation and a therapeutic polypeptide.

Applicants respectfully submit that the vectors of Gunzburg and the '775 Patent do not have this structure, and, as such, cannot provide this function. Gunzburg, for example, discloses either the wild type MMTV retrovirus or various plasmid-based vectors. Applicants respectfully submit that all of the viruses and vectors of Gunzburg have complete U3 sequences, and thus do not have a 3' U3 deletion.

Applicants further respectfully submit that while the '775 Patent teaches some vectors that have 3' U3 deletions, these vectors either do not have a polylinker sequence comprising at least one unique restriction site into which is inserted one or more non-coding sequences selected from regulatory elements and promoters (*see e.g.*, Figure 2C of the '775 Patent) or, if there is a promoter in the 3' U3 region, that promoter is operatively linked in the vector itself to the coding sequence it is intended to regulate.

These embodiments are exemplified by the vectors depicted in Figures 3, 4, 5B, 7A, 9, and 10. Thus, applicants respectfully submit that the vectors of the '775 Patent do not have the structure of the instantly claimed vectors. Accordingly, the Patent Office's assertion that the tissue-specific promoter that replaces the 3' LTR and the B and/or T cell active promoter encoding Sag is the only difference between the claimed

vectors and the vectors cited in the Gunzburg and '775 Patent is believed to be inaccurate.

Furthermore, applicants respectfully submit that the Patent Office must consider not only the elements that the claimed vectors and the vectors of the Gunzburg reference and the '775 Patent might share, but also how these elements are arranged in the vectors, the purposes of these elements in the vectors, and also what additional components the vectors of the cited references contain. Stated another way, applicants respectfully submit that the Patent Office must take the teachings of the cited references as a whole, and as such it is improper for the Patent Office to pick and choose only those claim elements that appear to be disclosed in the cited references while neglecting to consider the clear structural differences between the claimed vectors and the vectors disclosed in the cited references.

For example, applicants respectfully submit that only the '775 Patent teaches any vectors with 3' U3 deletions, and in each case where there is a 3' U3 deletion, this deletion is either maintained in the vector or is the site for cloning a minigene (*i.e.*, a promoter operatively linked to a coding sequence). This is in contrast to the vectors of claim 5, which recite a 3' U3 deletion which is replaced by a polylinker into which a regulatory element or promoter only has been cloned.

In summary, applicants respectfully submit that the Patent Office's assertion that the difference between the claimed vectors and the vectors disclosed in the cited references is the tissue specific promoter that replaces the 3' LTR and the B and/or T cell active promoter is not supported by close scrutiny of the Gunzburg reference and the '775 Patent. Thus, applicants respectfully submit that this assertion does not support the instant rejection of claims 5, 8, and 22-25 under 35 U.S.C. § 103(a).

In response to the applicants' arguments made in the amendment submitted December 13, 2004, the Patent Office asserts the following:

> The insertion of a functioning promoter (as applicant states would normally be present) at this defective site ensures expression of a heterologous gene upstream of the body of the vector after the virus is reverse transcribed. The replacement of the wild type promoter for a promoter that is more specific to the heterologous gene insert would have been *prima facie* obvious to one of ordinary skill in the art at the

> time the invention was made to restore normal virus replication, control the amount of gene expression and ensure that the gene of interest is only expressed in specifically targeted sites, as evidenced by the teachings of Vile *et al*.

Official Action at page 4.

Applicants respectfully traverse these assertions on several bases. First, the Patent Office asserts that "insertion of a functioning promoter... at this defective site ensures expression of a heterologous gene upstream of the body of the vector once the virus is reverse transcribed" (Official Action at page 4; emphasis added). Applicants respectfully submit that "expression of a heterologous gene upstream of the body of the vector" is not what is being claimed in the instant application. Applicants respectfully submit that claim 5 recites a retroviral vector wherein the regulatory elements and/or promoter express a heterologous gene present within the body of the vector after promoter conversion.

Applicants further respectfully submit that there is no disclosure in the '775 Patent, Gunzburg, and/or Vile of vectors that include (1) a 3' U3 deletion; (2) a polylinker sequence comprising at least one unique restriction site into which is inserted one or more non-coding sequences selected from regulatory elements and promoters cloned into the 3' U3 deletion; and (3) a coding sequence present within the body of the vector that comes under the transcriptional control of the one or more non-coding sequences after promoter conversion.

Thus, applicants respectfully submit that even assuming *arguendo* that the '775 Patent teaches a heterologous promoter cloned into a 3' U3 deletion, this promoter must always be operatively linked to a coding sequence in the vector, or a SIN vector will not result. Since the only vectors disclosed in the '775 Patent that contain 3' U3 deletions are SIN vectors, applicants respectfully submit that the disclosure of the '775 Patent teaches against cloning regulatory sequences and/or a promoter into the 3' U3 deletion and using the regulatory sequences and/or promoter to regulate expression of a coding sequence present within the body of the vector.

Stated another way, applicants respectfully submit that if regulatory sequences and/or a promoter are cloned into a 3' U3 deletion without being operably linked to a coding sequence, as is the case with the vectors of claim 5 of the instant application, then the vector will not be a SIN vector. Accordingly, applicants respectfully submit that the '775 Patent cannot be read to suggest the structure of the 3' LTR that is recited in the instant claims, and further respectfully submit that the combination of Gunzburg and the '775 Patent cannot be read to suggest such a structure.

Applicants respectfully submit that Vile does not cure this deficiency. Even assuming *arguendo* that Vile discloses retroviral vectors that express therapeutic genes from tissue-specific promoters, it does not overcome the lack of a teaching or suggestion in the combination of Gunzburg and the '775 Patent concerning the production of a retroviral vector with a heterologous promoter cloned into the 3' U3 region that can be used to regulate the expression of a therapeutic gene positioned in the body of the vector.

Therefore, applicants respectfully submit that the combination of Gunzburg, the '775 Patent, and Vile does not support a rejection of claims 5, 8, and 22-25 under 35 U.S.C. § 103(a). As such, applicants respectfully request that the instant rejection be withdrawn and the claims allowed at this time.

II.B. The Combination of Gunzburg, the '775 Patent, and Vile Does Not Disclose or Suggest a Retroviral Vector with Two Coding Sequences in the Body of the Vector

In addition to the deficiency discussed immediately hereinabove, applicants respectfully submit that the combination of Gunzburg, the '775 Patent, and Vile does not disclose or suggest a retroviral vector with a promoterless therapeutic gene coding sequence and a Sag peptide coding sequence operatively linked to a B and/or T cell specific promoter, wherein both of these coding sequences are present within the body of the vector. The Patent Office asserts, however, that since Claim 25 of the '775 patent is specifically drawn to a vector containing "a second, non-retroviral DNA sequence" within the body of the vector, the '775 Patent does teach a vector comprising two coding sequences within the body of the vector.

Applicants respectfully disagree. Applicants respectfully submit that even though Claim 25 of the '775 Patent recites a second, non-retroviral DNA sequence inserted in the body of the vector, this claim depends from claim 1, and that according to Claim 1, the first coding sequence is the transcription unit inserted only into the U3 region of the 3' LTR. Since the transcription unit is present in the 3' U3 region, it is not in the body of the vector, which is the region of the vector between the LTRs.

This is elaborated in the final clause of Claim 1 of the '775 Patent, which states that "infection of the eukaryotic cell with the retroviral vector results in the transcription unit being duplicated and appearing in both the 5' and 3' LTR of the retroviral vector". Based on the mechanics of the reverse transcription reaction, only sequences that are within the LTRs become duplicated, and therefore applicants respectfully submit that it is clear that the transcription unit recited in Claim 1 is not in the body of the vector.

Accordingly, applicants respectfully submit that the '775 Patent does not disclose two coding sequences present within the body of the vector. Further, applicants respectfully submit that the combination of Gunzburg, the '775 Patent and Vile does not disclose or suggest a retroviral vector with two coding sequences present within the body of the vector, wherein, upon promoter conversion following infection of a target cell, the expression of one of the two coding sequences is driven by a promoter originally located in the 3' U3 region of the vector, as is recited in Claim 5 of the instant application.

II.C. The Constructs Disclosed in the '775 Patent Do Not Have Sag Activity

The Patent Office further asserts that the construct of the '775 Patent "also has Sag activity since Gunzburg *et al.* teach that Sag is present in the U3 region of the 5' MMTV LTR, see Figure 1a." *See* Official Action, page 5. Applicants respectfully disagree. Applicants respectfully submit that the '775 Patent lists a number of retroviruses upon which the vectors described therein can be based. *See* '775 Patent, column 8, lines 51-58. The '775 Patent discloses the use of the avian sarcoma virus (AvSV), the murine sarcoma virus (MuSV), and murine leukemia viruses such as the mouse Maloney leukemia virus (M-MuLV). None of the vectors described in the '775

Patent contain a 5' mouse mammary tumour virus (MMTV) LTR, the LTR described in Gunzburg as containing the novel B cell specific promoter and the coding sequences for Sag in the U3 region of its LTR. Therefore, applicants respectfully submit that the '775 Patent could not be read in view of Gunzburg to suggest that the constructs of the '775 Patent have Sag activity. Further, Vile does not provide any suggestion that any of the elements of the vector constructs of the '775 Patent would encode a peptide with Sag activity.

II.D. There is No Motivation to Combine the References

Additionally, in order to establish a *prima facie* case of obviousness, there must be some motivation to combine the references as suggested by the Patent Office. According to the Patent Office, one of ordinary skill in the art would have been motivated to (a) express the heterologous therapeutic gene with a tissue specific promoter to express a gene of interest in a tissue of interest more specifically; (b) express Sag with a T and/or B cell specific promoter to optimize Sag expression in those cells for proliferation; and (c) express Sag from a T and/or B cell specific promoter to regulate its expression separately for the therapeutic gene.

Applicants respectfully submit that the Patent Office offers no support for the assertions presented hereinabove. Rather, the Patent Office presents only conclusory statements concerning these asserted motivations. As such, it appears that the motivations presented amount to no more than what one of ordinary skill in the art could have done. Applicants respectfully submit that according to MPEP 2143.01, the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness.

Indeed, applicants respectfully submit that the Patent Office has employed an impermissible hindsight reconstruction of the references to arrive at the instant rejection, and as such, has not presented a *prima facie* case of obviousness of claim 5 over the combination of Gunzburg, the '775 Patent, and Vile.

And finally, applicants respectfully submit that there can be no motivation to combine Gunzburg, the '775 Patent, and Vile because the '775 Patent discloses self-

inactivating vectors and the instantly claimed vectors are not self-inactivating. According to MPEP 2143.01, "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious" (*citing In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)).

To elaborate, applicants respectfully submit that the deletion of the 3' U3 sequences in the instantly claimed vectors results in the regulatory sequences and/or the promoter cloned into the deleted region being capable of regulating the transcription of the therapeutic gene present within the body of the vector. This principle, referred to in the instant specification as "promoter conversion", is a feature of a non-self-inactivating vector. Applicants respectfully submit that by definition, a self-inactivating vector such as those disclosed in the '775 Patent cannot undergo promoter conversion resulting in a coding sequence present within the body of the vector coming under the transcriptional control of a regulatory sequence or promoter present in the 3' U3 region. Gunzburg and Vile do not cure this deficiency.

Thus, applicants respectfully submit that the Patent Office's proposed combination of Gunzburg, the '775 Patent, and Vile is proscribed by MPEP 2143.01, and as such, does not support a *prima facie* case of obviousness of claim 5.

II.E. Summary

Accordingly, with respect to the instant rejection of independent Claim 5 under 35 U.S.C. § 103(a) over Gunzburg, the '775 Patent, and Vile, applicants respectfully submit that the cited combination does not support a *prima facie* case of obviousness for several reasons. First, the references do not disclose retroviral vectors that contain partial 3' U3 deletions into which a polylinker and a promoter and/or a regulatory element(s) has been inserted; wherein after infection of a target cell, a coding sequence present in the body of the vector becomes operatively linked to the promoter and/or regulatory sequence(s), and the promoter and/or regulatory sequences then regulate expression of the coding sequences present within the body of the vector in said target cell. Second, the references do not provide a vector containing two coding

sequences within the body of the vector, one encoding a therapeutic peptide and one encoding a peptide with Sag activity. Finally, there is no motivation to combine the cited references because one of ordinary skill in the art would not look to the '775 Patent to design a retroviral vector that is not a self-inactivating vector. Applicants respectfully submit that it is improper to combine the cited references to arrive at the vector described in Claim 5, because doing so would change the principle of operation of the vector described by the '775 patent.

Thus, applicants respectfully request that the instant rejection of Claim 5 under 35 U.S.C. § 103(a) over the combination of Gunzburg, the '775 Patent, and Vile be withdrawn. Claims 8 and 22-25 depend from claim 5, and, thus, claims 8 and 22-25 also are believed to be patentably distinguished over the cited combination. Therefore, applicants respectfully submit that claims 5, 8, and 22-25 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, applicants respectfully submit that claims 5, 8, and 22-25 are in condition for allowance at this time, and respectfully solicit a Notice of Allowance to that effect.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

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DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
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